Summary of Substance of the Interview

The Interview Summary form provides a recordation of the substance of the interview, and Applicants submit that this recordation of the substance of the interview is substantially complete. In addition to what is summarized on the Interview Summary form, Applicants' representative pointed out that two of the references cited by the Examiner on Form PTO-892, i.e., U.S. Patent Nos. 4,514,414 and 4,931,450, had already been brought to the Examiner's attention with the Information Disclosure Statement filed June 4, 2001, and that a document also submitted with this Information Disclosure Statement, i.e., EP 0 374 801 A2, provides evidence that the β-homoproline compounds mentioned in one of the cited references (SONNEWALD) are compounds having a 3-substituted pyrrolidine ring, not a 2-substituted ring as asserted in the outstanding Office Action. Also, the Examiner explained that the suggestion to eliminate heteroaryl as meaning for R^1 to R^7 was not because of any prior art the Examiner was aware of, but merely in order to facilitate searching for potentially conflicting prior art and to ensure an as complete search as possible.

Summary of Amendments

By the foregoing amendments claims 57 and 58 are canceled and claims 31, 32 and 59 are amended, whereby claims 31-56 and 59-61 are pending in the present application. Claims 31 and 59 are independent claims. Except for the deletions suggested by the

Examiner during the interview for the reasons set forth above in the section "Summary of Substance of the Interview", the amendments to the claims are of purely editorial nature and have only been made to eliminate some linguistic issues.

It is noted that the cancellation of claims 57 and 58 and the amendments to claims 31, 32 and 59 are without prejudice or disclaimer, and Applicants expressly reserve the right to prosecute the subject matter of the canceled claims as well as any of the subject matter which no longer is literally encompassed by the amended claims in one or more divisional and/or continuation applications.

Summary of Office Action

Claims 31-61 continue to be rejected under 35 U.S.C.§ 103(a) as being allegedly unpatentable over Bondinell et al., U.S. Patent No. 4,514,414 (hereafter "BONDINELL") in view of Sonnewald, U.S. Patent No. 4,931,450 (hereafter "SONNEWALD") and Ali et al., CAPLUS data base No. 102: 160041 (hereafter "ALI").

Response to Rejection

In the present Office Action, claims 31-61 are rejected under 35 U.S.C.§ 103(a) as being allegedly unpatentable over BONDINELL in view of SONNEWALD and ALI for the reasons given in the Office Action mailed August 9, 2002. In the Office Action of August

9, 2002, the Examiner essentially argued that BONDINELL discloses compounds which are structurally similar to some of the claimed compounds, the difference between these compounds being in the position of the substituent on the pyrrolidine ring, i.e., 2-position in the case of the claimed compounds, and 3-position in the case of the compounds of the reference. Furthermore, the rejection alleged that SONNEWALD and ALI teach that, in compounds homologous to those disclosed in BONDINELL, there is no difference in biological activity between 2-substitution and 3-substitution, wherefore a person of ordinary skill in the art would allegedly have expected that compounds which differ from those of BONDINELL with respect to the position of the substituent (2- vs. 3-), i.e., compounds of the present invention, would have a GABA inhibitory activity similar to that of the BONDINELL compounds. In an attempt to support the allegation with respect to SONNEWALD, copies from the CAS registry allegedly showing the structures of nipecotic acid and homoproline have been attached to the present Office Action.

Applicants submit that the rejection is apparently based on an incorrect understanding regarding the structure of "homoproline". Accordingly, for this reason alone the rejection cannot be maintained.

In particular, the understanding underlying the present rejection appears to be that SONNEWALD allegedly suggests that both compounds having a 3-substituted nitrogen containing ring (i.e., derivatives of nipecotic acid) and corresponding compounds having a

2-substituted ring (i.e., derivatives of "homoproline") have GABA uptake inhibitory activity.

Based on this (mis)understanding, the rejection essentially alleges that one of ordinary skill in the art would have been motivated to modify the 3-substituted compounds of BONDINELL by changing the 3-substitution to a 2-substitution like in the compounds according to the present invention.

As already pointed out during the interview, the "homoproline" compounds of SONNEWALD relied on by the Examiner actually are derivatives of β-homoproline. Furthermore, β-homoproline features a **3**-substituted pyrrolidine ring, not a **2**-substituted pyrrolidine ring as apparently assumed by the Examiner. Support for the correct structure of β-homoproline can be found in, e.g., EP 0 374 801 A2, a document submitted with the Information Disclosure Statement filed June 4, 2001. One of the inventors mentioned on the face of this document is Ursula Sonnewald, i.e., the inventor of the SONNEWALD reference. At page 2, lines 28/29 it is expressly stated that "[n]ipecotic acid is piperidine-3-carboxylic acid, guvacine is 1,2,5,6-tetrahydropyridine-3-carboxylic acid and homo-β-proline [i.e., β-homoproline] is pyrrolidine-3-acetic acid". It is noted that the specific compounds mentioned in columns 3-6 of SONNEWALD referred to in the rejection exclusively are derivatives of guvacine, nipecotic acid and β-homoproline, i.e., all are derivatives of compounds which have a 3-substituted nitrogen containing ring. This is in conformity with the fact that the 3-butenyl compounds of formula (I) as depicted in, e.g., column 1 and claim

1 of SONNEWALD do not have any 2-substituted nitrogen-containing ring as group R^3. In particular, R^3 in said formula (I) is 3-carboxypiperid-1-yl, 3-carboxy-1,2,5,6-tetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl, or the corresponding amide, lower alkyl ester or salt group (e.g., col. 1, lines 29-32). In view of the foregoing, it is respectfully submitted that even a combination of the teachings of BONDINELL and SONNEWALD would not have resulted in the compounds according to the present invention, all of which comprise a 2-substituted nitrogen containing ring.

Essentially the same arguments apply to a combination of BONDINELL and ALI. As noted in the response filed November 11, 2002, it appears that this document does not specifically refer to compounds having a 2-substituted pyrrolidine ring. For example, the compound of formula I as depicted in ALI is a 3-substituted piperidinecarboxylic acid. While ALI makes reference also to "pyrrolidineacetic acids", this document does not indicate at which position the pyrrolidine ring structure of these compounds is substituted by the carboxymethyl group (2- or 3-position). Moreover, it is to be noted that the authors of ALI include William E. Bondinell and John J. Lafferty, i.e., two of the inventors of BONDINELL. Accordingly, it appears reasonable to assume that the full disclosure of ALI (cited by the Examiner only in the form of an abstract), published in 1985, is similar to that of BONDINELL (filed October 25, 1982), which only shows 3-substituted compounds.

In view of the foregoing, it is submitted that the rejection of claims 31-61 under 35

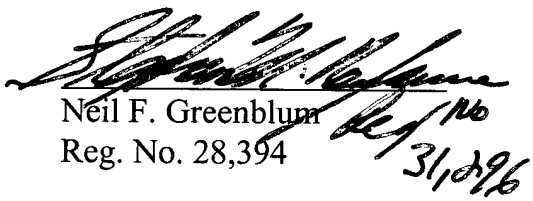
U.S.C.§ 103(a) is not justified, wherefore withdrawal thereof is respectfully requested.

CONCLUSION

In view of the foregoing, it is believed that all of the claims in this application are in condition for allowance, which action is respectfully requested.

If any issues yet remain which can be resolved by a telephone conference, the Examiner is respectfully invited to contact the undersigned at the number given below.

Respectfully submitted,
K. WANNER et al.



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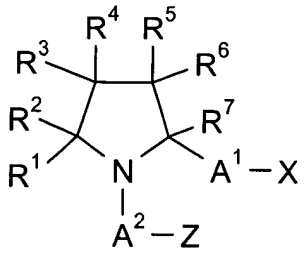
APPENDIX

Marked-up copy of amended claims

31. (Twice Amended) A compound of formula (I)



(I)

wherein

R^1 to R^7 are independently selected from H, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, optionally substituted aryl [or heteroaryl], OH, halogen, CN, OR^{12}, SR^{12}, COR^{12}, $COOR^{12}$, SOR^{12}, SO_2R^{12}, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, $SO_2NR^{13}R^{14}$, where R^{13} and R^{14} are independently selected from H and C_{1-3} alkyl and R^{12} represents C_{1-6} alkyl; two of R^1 to R^7, together with the atoms connecting them, [each may] optionally form a 3- to 6-membered ring system [, which ring system may contain one or more heteroatoms]; at least one of the pairs R^1 and R^2; R^3 and R^4; and R^5 and R^6 [may be] is optionally replaced by an optionally substituted alkylidene group or =O; and two of R^1 to R^7 which are positioned at adjacent carbon atoms [may each be] are optionally replaced by a C-C bond;

A^1 is selected from $(-CR^8R^9-)_n$, optionally substituted C_{3-6} cycloalkylene and a combination of these groups, R^8 and R^9 being independently selected from H, C_{1-6} alkyl, halogen, OH, OR^{12} and $NR^{13}R^{14}$ [and], where for $n \geq 2$, R^8 and R^9 [may be] are the same or

different in each group and two groups selected from R^8 and R^9 at adjacent C atoms [may be] are optionally replaced by a C-C bond, and a group -O- or -CO- [may be] is optionally positioned between two adjacent groups CR^8R^9; and wherein one of R^8 and R^9 [may be] is optionally combined with one of R^1 to R^7 to form a 5- to 7-membered ring structure; and n = 1, 2, 3 or 4;

X is selected from COOM and groups which [can be] are capable of being converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H, C_{1-2} alkyl and halogen; where for m ≥ 2 the groups R^{10} and R^{11} [may be] are the same or different in each group, a group -O- or -S- [may be] is optionally positioned between two adjacent groups $-CR^{10}R^{11}-$, and two groups selected from R^{10} and R^{11} at adjacent C atoms [may be] are optionally replaced by a C-C bond; and wherein one of R^{10} and R^{11} [may be] is optionally combined with one of R^1 to R^9 to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

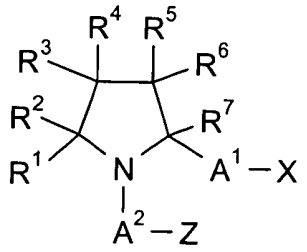
Z is selected from Y_3C-O-, $Y_2C{=}CR^{15}$- and Y_2C=N-O-, where R^{15} is selected from H, C_{1-3} alkyl or halogen and the groups Y are independently selected from optionally substituted C_{6-12} aryl and optionally substituted C heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y [may be] are optionally linked

by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from [-O-, -S-, -NH-, -O-,] -CH=CH-, [-CH=N-,] -CH_2- and -CH_2CH_2-;

[as well as] and the individual stereoisomers of these compounds.

32. (Amended) The compound of claim 31, wherein R^7 is hydrogen and R^1 to R^6 are independently selected from hydrogen, optionally substituted C_{1-3} alkyl, halogen, OH, CN, and optionally substituted phenyl [and optionally substituted heteroaryl having 5 to 10 ring members and one or two heteroatoms selected from O, N and S].

59. (Twice Amended) A pharmaceutical composition comprising at least one of a pharmaceutically acceptable carrier and a pharmaceutically acceptable excipient and at least one compound of formula (I):



(I)

wherein

R^1 to R^7 are independently selected from H, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, optionally substituted aryl [or heteroaryl], OH, halogen, CN, OR^{12},

SR^{12}, COR^{12}, $COOR^{12}$, SOR^{12}, SO_2R^{12}, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, $SO_2NR^{13}R^{14}$, where R^{13} and R^{14} are independently selected from H and C_{1-3} alkyl and R^{12} represents C_{1-6} alkyl; two of R^1 to R^7, together with the atoms connecting them, [each may] optionally form a 3- to 6-membered ring system [, which ring system may contain one or more heteroatoms]; at least one of the pairs R^1 and R^2; R^3 and R^4; and R^5 and R^6 [may be] is optionally replaced by an optionally substituted alkylidene group or =O; and two of R^1 to R^7 which are positioned at adjacent carbon atoms [may each be] are optionally replaced by a C-C bond;

A^1 is selected from $(-CR^8R^9-)_n$, optionally substituted C_{3-6} cycloalkylene and a combination of these groups, R^8 and R^9 being independently selected from H, C_{1-6} alkyl, halogen, OH, OR^{12} and $NR^{13}R^{14}$ [and], where for $n \geq 2$, R^8 and R^9 [may be] are the same or different in each group and two groups selected from R^8 and R^9 at adjacent C atoms [may be] are optionally replaced by a C-C bond, and a group -O- or -CO- [may be] is optionally positioned between two adjacent groups CR^8R^9; and wherein one of R^8 and R^9 [may be] is optionally combined with one of R^1 to R^7 to form a 5- to 7-membered ring structure; and n = 1, 2, 3 or 4;

X is selected from COOM and groups which [can be] are capable of being converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H, C_{1-2} alkyl and

halogen; where for m ≥ 2 the groups R^{10} and R^{11} [may be] are the same or different in each group, a group -O- or -S- [may be] is optionally positioned between two adjacent groups $-CR^{10}R^{11}-$, and two groups selected from R^{10} and R^{11} at adjacent C atoms [may be] are optionally replaced by a C-C bond; and wherein one of R^{10} and R^{11} [may be] is optionally combined with one of R^1 to R^9 to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from Y_3C-O-, $Y_2C=CR^{15}-$ and $Y_2C=N-O-$, where R^{15} is selected from H, C_{1-3} alkyl or halogen and the groups Y are independently selected from optionally substituted C_{6-12} aryl and optionally substituted C_{2-5} heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y [may be] are optionally linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from [-O-, -S-, -NH-, -O-,] -CH=CH-, [-CH=N-,] $-CH_2-$ and $-CH_2CH_2-$.